

In brief, the inventors have discovered that “benign or malignancy” or “degree of malignancy” of thyroid tumor can be detected on the basis of a ratio of “the total amount of thyroglobulin in cells or blood” relative to “the amount of thyroglobulin having the specific sugar chain structure” or “the amount of thyroglobulin having a sugar chain structure other than the specific sugar chain structure,” and on the basis of this finding, the method for measuring separately “the total amount of thyroglobulin in cells or blood” and “the amount of specific thyroglobulin having the specific sugar chain structure” has been established.

In the claimed invention, the total thyroglobulin amount can be measured by using the agent (protein) capable of binding to all thyroglobulin regardless of the sugar chain structure, namely capable of binding to the constant region of thyroglobulin, the constant region being the region contained in common thyroglobulin regardless of their sugar chain structure, and then the amount of specific thyroglobulin having the specific sugar chain structure can be measured by allowing the agent (protein) capable of binding only to the specific sugar chain structure to react with the total thyroglobulin separated in the above process step.

In summary, the disclosures in the references now cited are all substantially or materially concerned with specifying or analyzing sugar chain structures of thyroglobulin by *using lectin(s) only*. It is impossible to measure the total thyroglobulin by *using only lectin(s)*, because the lectin(s) is “the protein binding to a specific sugar chain structure” of thyroglobulin as mentioned in the present specification on page 6, lines 7-24. Actually, there is found no disclosure nor

suggestion about “measuring an amount of the *total* thyroglobulin” and “measuring the *specific thyroglobulin* having the specific sugar chain structure” separately. There is also no disclosure nor suggestion about the determination of “benign or malignancy” or “the degree of malignancy” on the basis of the claimed ratio of the above two measuring results.

Claims 1-18 stand rejected under 35 U.S.C. §102(a) as being anticipated by **Maruyama et al., Arch. Pathol Med, Vol. 122**, August 1998. This reference is published after the priority date (June 30, 1998) of the application for which the applicants have claimed priority. the rejection is now moot.

Claims 1-2 and 6-7 stand rejected under 35 U.S.C. §102(b) as being anticipated by **SAR van de Graaf et al., European Journal of Endocrinology**, 1997. This reference discloses the following: cDNA fragments of human Tg are transected in cell line, and sugar chain structure of the Tg protein fragments expressed by thus obtained transformat are identified by reacting *with lectins only*, and the results are compared with native Tg protein fragments. Namely, what this reference discloses is to identify or analyze the sugar chain structure of Tg by *using lectins only*. However, there is no disclosure found or suggested on measurement of an amount of Tg. The determination of malignancy of thyroid tumor is not disclosed.

Claims 1-18 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Hanham et al. Biochemica et Biophysica Acta**, Vol. 884, 1986. Purified Tg treated with or without enzyme is applied to lectin affinity electrophoresis using agarose gels containing *lectin such as* ConA, RCA, LCA etc. *only*, whereby the sugar chain structure is identified. this reference is also concerned with, just like **Simore AR van de Graaf et al.**, identification of sugar chain structures. No disclosure of measurement of Tg nor determination of malignancy of thyroid tumor is made.

Claims 1-3, 5-12 and 14-18 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Tarutani et al., Journal of Biochemistry**, Vol. 98, pages 851-857, 1985. Thyroid tissues are sliced and soluble proteins are extracted (p. 852, "Materials and Methods, Thyroid Glands"). The obtained extract is passed through a column packed with ConA, etc., whereby ingredients contained in the extract are separated on a chromatography. And, it is predicted that carbohydrate structures are different between normal Tg and tumor Tg.

In the disclosure, *only the single use of lectin(s) is disclosed*. Actually, there is found no concrete disclosure on the measurement of the total amount of Tg in a sample nor the measurement of the amount of Tg having specific carbohydrate structure. Additionally, no disclosure concerning using two kinds of proteins (e.g., antibody) for the measurement is found. Needless to say, there is found no disclosure or suggestion concerning determination of malignancy or thyroid tumor.

Claims 1-3, 6-12 and 15-18 stand rejected under 35 U.S.C. §1029b) as being anticipated by **Wang et al., Chung-hua Ping Li Hseuh Tsa Chin**, Vol. 19, No. 2, pages 90-93. Tg of thyroid carcinoma is investigated by histological and immunohistochemical techniques *using a lectin only*, and thyroid tumor are divided into three categories by the lectin binding property. It is considered that different lectin has a selective binding activity to various type of thyroid carcinoma and normal thyroid cells. But in the reference, just like as other references, there is found no disclosure nor suggestion on measurement of amount of Tg nor determination of a malignancy of thyroid tumor.

The method and reagent as now claimed by the applicants has not hereto before been performed or known. The prior art references do not suggest measuring the species in solution as the applicants are now claiming. Hence the prior art does not suggest to make a determination of malignancy based on the measurement of these species. Because the combination of the references do not teach or suggest the applicants' invention as now claimed, it is respectfully requested that the claims be allowed.

If, for any reason, it is believed that this application is not now in condition for allowance, the Examiner is requested to contact Applicant's undersigned attorney at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

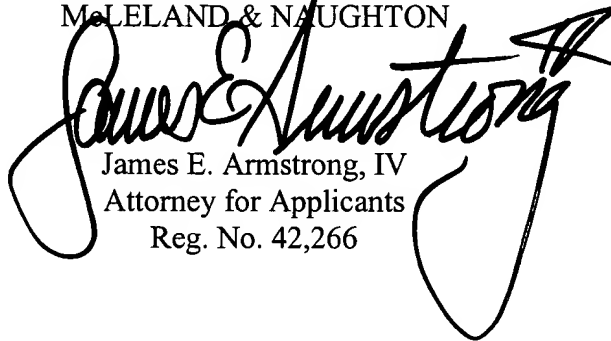
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In the event that this paper is not timely filed, Applicant respectfully petitions for an appropriate extension of time. The fees for such an extension or any other fees which may be due with respect to this paper, may be charged to Deposit Account No. 01-2340.

Respectfully submitted,

ARMSTRONG, WESTERMAN, HATTORI,  
MCLELAND & NAUGHTON

A large, stylized handwritten signature in black ink, which appears to read "James E. Armstrong, IV". The signature is written over the printed name and title of the attorney.

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